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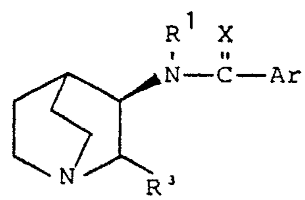
(54) **Memory enhancing-R-N-(1-azabicyclo[2.2.2] oct-3-yl) benzamides and thiobenzamides.**

(57) Compounds of general formula I



(I)

wherein:
X represents oxygen or sulphur;
each of R^1 and R^3 independently represents hydrogen or a C_1-C_4 alkyl group;
Ar represents:
a phenyl ring optionally substituted by one, two or three C_1-C_4 alkoxy groups and/or by one or two halogen atoms;
a phenyl ring of the general formula

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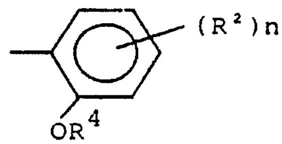
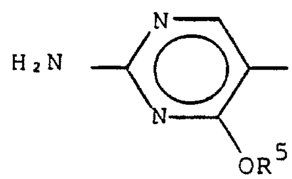


wherein R^2 represents halogen, 4,5-benzo, C_1-C_8 alkoxy, C_1-C_4 alkylcarbonyl or Am, wherein Am represents amino, methylamino or dimethylamino,
R^4 represents C_1-C_8 alkyl,
n is 1 or 2; or
a pyrimidinyl moiety of the general formula



wherein R^5 is C_1-C_4 alkyl;
and their N-oxides and pharmaceutically acceptable salts are useful as memory- and/or learning-enhancing agents. A preferred compound is R-(+)-4-amino-N-(1-azabicyclo[2.2.2]oct-3-yl)-5-chloro-2-methoxybenzamide.

MEMORY ENHANCING-R-N-(1-AZABICYCLO[2.2.2]OCT-3-YL) BENZAMIDES AND THIOBENAMIDES

The present invention relates to the use of certain optical isomers of N-(3-quinuclidinyl)benzamides and thiobenzamides, namely R-N-(3-quinuclidinyl)-benzamides and thiobenzamides, otherwise known as R-N-(1-azabicyclo[2.2.2]oct-3-yl)-benzamides and thiobenzamides, which have been observed to exhibit memory enhancing properties in warm blooded animals.

Quinuclidine analogues of sulpiride were prepared and studied by Mikhlina, E. E. et al as reported in Khim-Farmatsevt. Zh. 10, No. 11, 56-60 (1976); C.A. 85: 155489r exemplified by the compound: 5-aminosulphonyl-N-(1-azabicyclo[2.2.2]oct-3-yl)-2-methoxybenzamide. This compound and others in the series were reported by the authors not to have antiemetic activity. The above named compound was reported in USSR Patent SU-A-414261 to have neuroleptic activity.

Syntheses of 4-amino-N-(1-azabicyclo[2.2.2]oct-3-yl)benzamide and N-(1-azabicyclo[2.2.2]oct-3-yl)-benzamide were reported by Mikhlina, E. E. et al in Khim-Farmatsevt. Zh. 7, 20-24 (1974); C.A. 79, 146458a and the latter in Khim.Geterosikl. Soedin., Akad. Nauk. Latv. SSR 243-9 (1966); C.A. 65: 2220b. These compounds were reported to exhibit hypotensive, narcotic and ganglionic stimulation and blocking activities.

Synthesis of 4-amino-N-(1-azabicyclo[2.2.2]oct-3-yl)-3-chloro-5-trifluoromethylbenzamide was reported in DE-A- 2548968; C.A. 87, 68001c and in equivalently related US-A-4093734 from 4-amino-3-chloro-5-trifluoromethyl benzoic acid chloride and 3-aminoquinuclidine. The compound is in a class among pyrrolidinyl and piperidinyl benzamides which are said to be useful as anxiolytics, anticonvulsives, antiemetics and antiulcerogenics.

It is widely recognized that substituted benzamides are a class of drugs known to be effective in psychiatry and gastroenterology (Sulpiride and other Benzamides; International Workshop on Sulpiride and other benzamides, Florence, Feb. 17-18 (1978), Raven Press]. However, the R-N-(1-azabicyclo[2.2.2]oct-3-yl)-benzamides used in this invention have now been found to have marked memory enhancing properties.

EP-A-0099789 and FR-A-2529548 disclose racemic mixtures of N-(1-azabicyclo[2.2.2]oct-3-yl) benzamides and their use as gastrointestinal motility accelerators.

US-A-4593034 and EP-A-0158532 disclose the treatment of emesis caused by the administration of platinum anticancer drugs (such as cisplatin) by the use of racemic mixtures of 2-alkoxy-N-(1-azabicyclo-[2.2.2]oct-3-yl) benzamides or thiobenzamides.

EP-A-0201165 describes a large class of compounds, covering certain racemic mixtures of N-(1-azabicyclo[2.2.2]oct-3-yl) benzamides and reports that they are useful in the treatment of emesis, anxiety and/or irritable bowel syndrome (IBS).

EP-A-0190920 discloses the enhancement of memory or the treatment of memory deficiency by the administration of certain racemic mixtures of arylamido- and arylthioamido-azabicycloalkanes including racemic mixtures of N-(1-azabicyclo[2.2.2]oct-3-yl) benzamides.

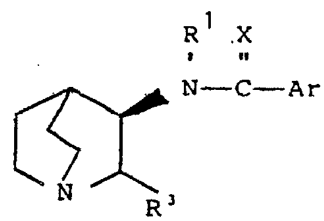
GB-A-2193633 discloses a large class of compounds, including N-(1-azabicyclo[2.2.2]oct-3-yl) benzamides for the treatment of stress-related psychiatric disorders, for increasing vigilance, for the treatment of rhinitis or serotonin-induced disorders, for increasing the bioavailability of other active agents and for nasal administration.

FR-A0-8701355 (filed 4th February 1987) discloses that S-enantiomers of the compounds disclosed in EP-A-0099789 increase the motility of certain areas of the gastrointestinal tract and inhibit emesis, particularly that induced by cisplatin.

EP-A0-87402321.1 (filed l6th October 1987) discloses that R-enantiomers of N-(1-azabicyclo[2.2.2]oct-3-yl) benzamides have anxiolytic activity.

It has now unexpectedly been discovered that the TR-enantiomers of various N-(1-azabicyclo[2.2.2]oct-3-yl)benzamides exhibit memory enhancing activity in warm blooded animals.

According to the present invention, there is provided the use of a compound of general formula I



(I)

wherein:

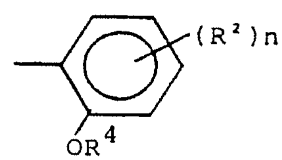
X represents oxygen or sulphur;

each of R^1 and R^3 independently represents hydrogen or a C_1-C_4 alkyl group;

Ar represents:

a phenyl ring optionally substituted by one, two or three C_1-C_4 alkoxy groups and/or by one or two halogen atoms;

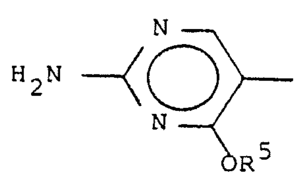
a phenyl ring of the general formula



wherein R^2 represents halogen, 4,5-benzo, C_1-C_8 alkoxy, C_1-C_4 alkylcarbonyl or Am, wherein Am represents amino, methylamino or dimethylamino,

R^4 represents C_1-C_8 alkyl n is 1 or 2; or

a pyrimidinyl moiety of the general formula



wherein R^5 is C_1-C_4 alkyl;

or an N-oxide and/or pharmaceutically acceptable salt thereof,

in the preparation of an agent for enhancing memory or learning.

The compound will generally be substantially free of the S-enantiomer.

Preferred compounds useful in the invention include those having one or more of the following features:

- each of R^1 and R^3 independently represents hydrogen, methyl or ethyl
- Ar represents 4-Am-5-chloro-2-methoxyphenyl.

A particularly preferred compound useful in the invention is R-(+)-4-amino-N-(1-azabicyclo[2.2.2]oct-3-yl)-5-chloro-2-methoxybenzamide whether as the free base or a salt (for example fumarate or hydrochloride).

In the further definition of symbols in the formulae hereof and where they appear elsewhere throughout this specification and the claims, terms have the following significance.

The term "C_1-C_8alkyl" as used herein includes straight and branched chain radicals of up to eight carbons inclusive and is exemplified by such groups as methyl, ethyl, propyl, isopropyl, butyl, amyl, hexyl, heptyl, and octyl radicals and the like. The term "C_1- C_8alkoxyl" has the formula -O-C_1-C_8alkyl. The terms "C_1-C_4alkyl" and "C_1-C_4alkoxyl" are to be construed as containing up to four carbon atoms accordingly.

The terms "halo" or "halogen" when referred to herein include fluorine, chlorine, bromine and iodine unless otherwise stated. Chlorine and bromine are preferred. "Pharmaceutically acceptable salts" include

the acid addition salts, hydrates, alcoholates and salts of the compounds, which salts are physiologically compatible in warm blooded animals. The acid addition salts may be formed by either strong or weak acids. Representative of strong acids are hydrochloric, sulphuric and phosphoric acids. Representative of weak acids are fumaric, maleic, succinic, oxalic, citric, tartaric, cyclohexamic and the like.

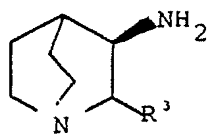
Protected amino groups used in synthesis are acetylamino or benzoylamino radicals and the like on the benzamide moiety mentioned hereinbelow in synthetic methods.

The optically active compounds (which term includes salts where the context so admits) useful in the invention may broadly speaking be prepared either by separation from racemates or other mixtures with the corresponding S-enantiomer or by asymmetric synthesis, as in EP-A0-87402321.1.

A process for the preparation of a compound of general formula I therefore comprises either

(1) separating a compound of general formula I from a mixture with its corresponding S-enantiomer; or

(2.1.1) coupling a 3 aminoquinuclidine of absolute configuration R general formula (II)



(II)

wherein R^3 is as defined for general formula (I) with an acid of general formula (III):

O
‖
HO-C-Ar (III)

wherein Ar is as defined for general formula (I); or

(2.1.2) reacting an R-3-aminoquinuclidine of general formula (II) with an acid derivative of general formula (IIIa)

O
‖
L-C-Ar (IIIa)

wherein Ar is as defined for general formula (I) and L is a leaving group; and

(2.1.3) optionally after step 2.1.1 or 2.1.2 converting a compound of general formula (I) so formed in which X represents an oxygen atom into a compound of general formula (I) in which X represents a sulphur atom; or

(2.2) when X represents a sulphur atom reacting an R-3-aminoquinuclidine of general formula (II) with an aldehyde ArCHO wherein Ar is as defined for general formula (I) and sulphur; or

(2.3) for an amino-substituted compound of general formula (I) reducing a corresponding nitro-substituted compound, and

(2.4) optionally after any of steps 1, 2.1.1, 2.1.2, 2.1.3, 2.2 and 2.3 converting a compound of general formula (I) so formed into another compound of general formula (I) or an N-oxide and/or salt thereof.

N-oxides can be prepared by treatment with a peracid such as m-chloroperbenzoic acid or hydrogen peroxide in an organic solvent such as methylene chloride at room temperature. Salts can be prepared as described above.

Process (1) may be achieved for example by recrystallisation of a salt formed with an optically active acid (for example an enantiomer of tartaric acid). By way of illustration, the following protocol may be followed for the resolution of N-(3-quinuclidinyl)-3-chlorobenzamide (N-(1-azabicyclo[2.2.2]oct-3-yl)-3-chlorobenzamide).

To the racemate in base form is added a solution of dextrorotatory L tartaric acid in methanol. The mixture obtained is brought to reflux, filtered when hot and left to cool. The precipitate is filtered and redissolved in boiling methanol. After cooling and filtration, the precipitate is dissolved in boiling methanol

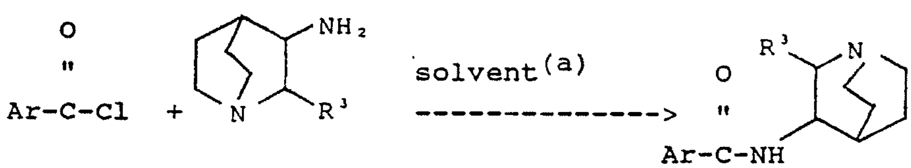
again. After cooling and filtration, the compound obtained is dissolved in water; the resulting aqueous solution is basified by means of sodium carbonate, extracted with chloroform, dried on sodium sulphate and filtered. The filtrate is evaporated. The product obtained is dissolved in acetone and hydrochloric ethanol (about 6N) is added; the precipitate obtained is filtered and recrystallized in ethanol. Thus, the dextrorotatory isomer is obtained.

The mother liquor of the first three recrystallizations in methanol and combined and evaporated. The residue is taken in water, and the resulting mixture is basified by means of sodium carbonate and then extracted with chloroform. The extract is dried on sodium or magnesium sulphate and filtered. The filtrate is evaporated. To the product is added a solution of laevorotatory D-tartaric acid in methanol. The mixture is brought to reflux, filtered when hot and the filtrate is cooled. The precipitate obtained is then filtered. This precipitate is dissolved in boiling methanol and the solution is filtered when hot. After the filtrate has cooled, the precipitate obtained is filtered. A precipitate is obtained which is dissolved in water. The solution is basified by means of sodium carbonate, extracted with chloroform and the extract is dried on sodium or magnesium sulphate. It is then filtered and the filtrate is then evaporated leaving a residue which is dissolved in acetone and hydrochloric ethanol (about 6N). The precipitate obtained is filtered and recrystallized in ethanol. In this way, the laevorotatory isomer is obtained.

Preparation of Benzamides

Racemates of compounds of Formula I and the corresponding R- or S-isomers are preparable by reacting a suitably activated benzoic acid derivative with 3-aminoquinuclidine to form the corresponding benzamide under a variety of conditions. Two general methods, A and B, are illustrated in the following equations:

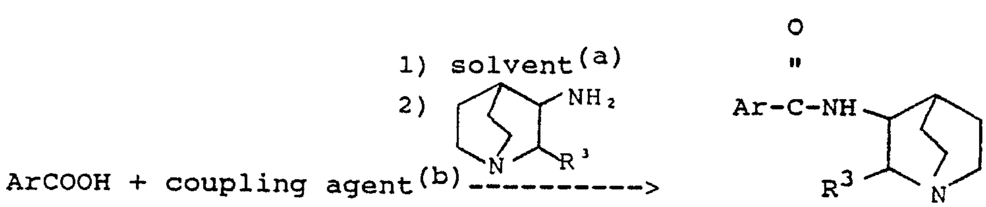
Method A, using an Acid Chloride



(a) Suitable solvents are organic solvents or a mixture of organic solvents and water; examples of organic solvents include chloroform and diethyl ether.

Method A is illustrated by Examples 5, 6, 7 and 9.

Method B, using a coupling agent



(a) e.g., tetrahydrofuran

(b) e.g., dicyclohexylcarbodiimide or 1,1′-carbonyldiimidazole

Method B is illustrated in Examples 1, 3 and 8 and 14.

Compounds wherein R_2 is primary amino may also be prepared from a compound prepared by

Methods A or B, wherein R_2 is nitro by catalytic reduction of the nitro compound.

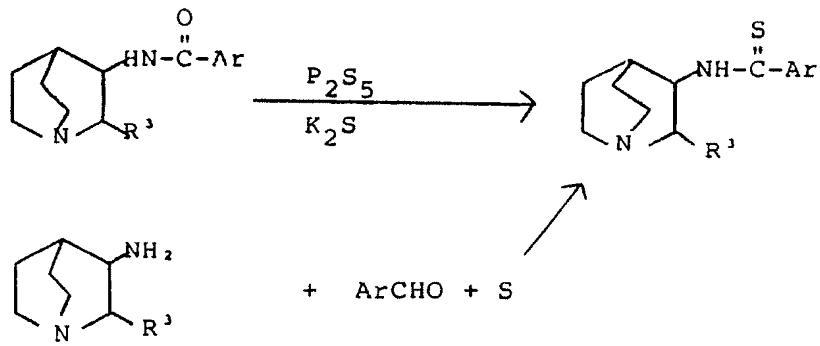
Alternatively, compounds wherein R_2 is amino may be prepared by procedures of Method A utilizing a starting benzoyl halide wherein the amino group has been protected, or they may be prepared from compounds prepared in Method A or B wherein R_2 is nitro and reducing the nitro radical to an amino radical.

Preferably, the compounds wherein R_2 is amino or methylamino are prepared by Method B.

The free base of any compound of Formula I from its acid addition salt may be regenerated by usual procedures of partitioning between dilute aqueous base and a suitable solvent, separating the solvent layer, drying and evaporating.

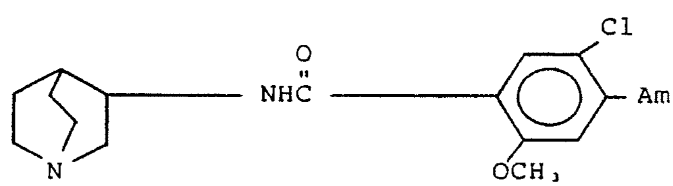
Preparation of Thiobenzamides

The preparation of the thiobenzamido compounds of Formula I′ may be accomplished by mixing and reacting a benzamido compound of Formula I with a mixture of phosphorus pentasulphide (P_2S_5) and potassium sulphide (K_2S) or by mixing and reacting 3-aminoquinuclidine with an appropriately substituted benzaldehyde and sulphur. The reaction sequences are illustrated by the following:



In these methods, compounds wherein R_2 is nitro may be reduced to compounds wherein R_2 is amino.

A preferred group of compounds encompassed by Formula I have the formula:



wherein Am is amino (i.e., $-NH_2$) or methylamino. As will be recognized from the above description, these compounds (Ic) are preferably prepared by Method B.

In process step 2.1.1 the coupling may be effected by means of a carbodiimide such as dicyclohexylcarbodiimide or 1,1′-carbonyldiimidazole.

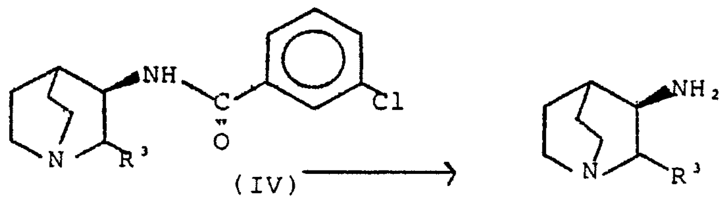
In process step 2.1.2 the leaving group L may be a halogen atom (such as chlorine) in which case the compound of general formula (IIIa) will be an acid halide.

In process step 2.1.3 the conversion of a compound of general formula (I) where X is an oxygen atom to a compound of general formula (I) where X is a sulphur atom may be effected by mixing and reacting with a mixture of phosphorus pentasulphide and potassium sulphide.

An R3-aminoquinuclidine of general formula (II) may be prepared by a number of different ways as follows. Although the following description is given primarily with reference to the case when R^3 is hydrogen (that is, when the 3-aminoquinuclidine moiety is otherwise unsubstituted), it is to be understood that it is equally applicable to cases where R^3 is an alkyl radical. Compounds of general formula (II) can be prepared by the reduction of the oxime of the corresponding 3-quinuclidinone by treatment with hydrogen and Raney

nickel. The oximes in turn are preparable by treatment of the corresponding 3-quinuclidinones with hydroxylamine hydrochloride in the presence of base. The 2-alkyl-3-quinuclidinones can be prepared by reduction with palladium-on-carbon; their production is described in J. Het. Chem. 3 109 (1966).

First, a compound of general formula (II) may be obtained by hydrolysing an optionally substituted benzamide such as an R-N-(3-quinuclidinyl)-3-chlorobenzamide of general formula (IV):

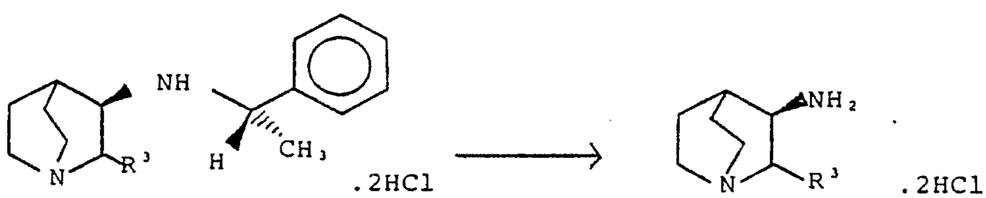


Hydrolysis may be achieved by dilute acid, such as dilute hydrochloric acid, in which case the dihydrochloride salt of compound (II) will result.

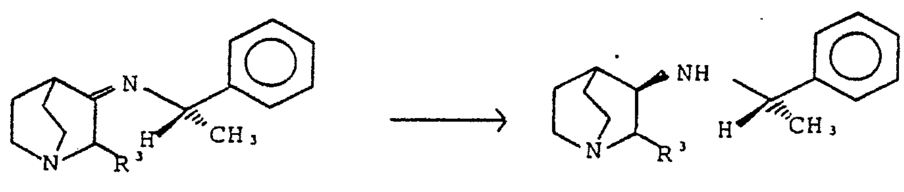
R-N-(3-quinuclidinyl)-3-chlorobenzamides of general formula (IV) may be separated from a racemic mixture by crystallization of the diastereoisomeric salts obtained by the action of L-tartaric acid. Treatment of the appropriately separated salt with base yields the free R-N-(3-quinuclidinyl)-3-chlorobenzamide.

A racemic mixture of R- and S-N-(3-quinuclidinyl)-3-chlorobenzamides may be obtained by condensing a racemic 3-aminoquinuclidine with a reactive derivative of 3-chlorobenzoic acid or with 3-chlorobenzoic acid itself and a coupling agent such as a carbodiimide. Racemic 3-aminoquinuclidines may be obtained by the action of hydroxylamine or hydrochloride followed by base (such as sodium ethoxide) on 3-quinuclidinones and reduction of the corresponding oxime with hydrogen and Raney nickel, as an example. If necessary 3-quinuclidinones may be prepared by oxidising 3-quinuclidinols, whose preparation is described in J. Am. Chem. Soc **74**, 2215 (1952).

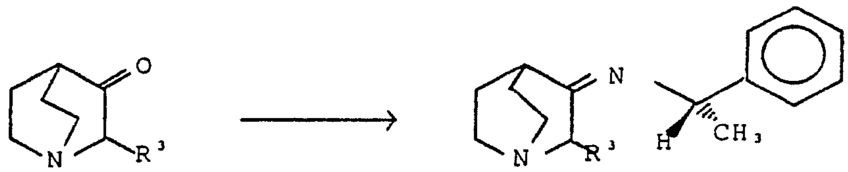
Secondly, a compound of general formula (II) may be produced by debenzylating S-N-(alpha-methylbenzyl)-R-3- aminoquinuclidine by hydrogenolysis in an acid medium in the presence of a catalyst, such as palladium on carbon.



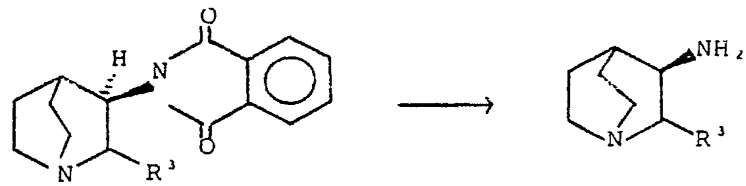
S-N-(alpha-methylbenzyl)-R-3-aminoquinuclidine may be obtained by the reduction of S-N-(alpha-methylbenzyl)3-quinuclidinimine by hydrogenolysis in the presence of a catalyst such as platinum oxide or by a borohydride such as potassium borohydride.



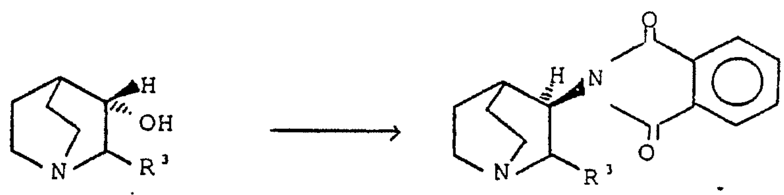
In turn, the S-N-(alpha-methylbenzyl)-3-quinuclidinimine may be obtained by treating 3-quinuclidinone with S-alpha-methylbenzylamine.



Thirdly, R-3-aminoquinuclidine may be prepared, as the dichloride, from R-phthalimido-3-quinuclidine by treating the starting material with hydrazine and then with hydrochloric acid.



In turn, R-phthalimido-3-quinuclidine can be obtained from S-3-quinuclidinol, which is known from Eur. J. Med Chem (1979) **14**, 111-114, by reacting the alcohol with phthalimide in the presence of triphenylphosphine and ethyl azodicarboxylate.



The mechanism of this reaction involves an inversion of configuration of the hydroxy-bearing carbon atom (J. Am. Chem Soc (1972) **84**, 679).

A compound of general formula I may therefore be used in pharmaceutical and/or veterinary medicine, in the enhancement of memory or learning.

Compounds of general formula I will frequently be used in a pharmaceutical and/or veterinary composition comprising (a) a compound of general formula I and (b) a suitable carrier therefor.

The memory/learning enhancement activity was determined by the method of Costall et al details of which are to be found in the pharmacology examples later in this specification. In brief, the method involves seeing whether the compound under test shortens the time taken for mice to learn to find there way from an averse, white, brightly-lit area of the test environment to a more acceptable, dark, dimly-lit area which communicates with the bright area by means of an interconnecting door.

It is therefore a primary object to provide a method of enhancing memory and learning, by the administration of an effective dose of certain R-N-(1-azabicyclo[2.2.2]oct-3-yl)benzamides and thiobenzamides.

A still further object is to provide means for enhancing memory and/or learning.

The invention will now be illustrated by the following non-limiting examples.

EXAMPLE 1

R(+)-4-Amino-N-(1-azabicyclo[2.2.2]oct-3-yl)-5-chloro2-methoxybenzamide, fumarate [1:1].

(R(+)-4-Amino-5-chloro-2-methoxy-N-(quinuclidin-3-yl)benzamide, fumarate [1:1]).

In a closed system equipped with an oil bubbler, 30ml of tetrahydrofuran was added to a mixture of 4-amino-5-chloro-2-methoxybenzoic acid, 2.02g, (0.010 mole) and 1,1′-carbonyldiimidazole, 1.62g (0.010 mole) with stirring. When evolution of carbon dioxide ceased, nitrogen was bubbled through the reaction mixture for 1 hr. A solution of 3-aminoquinuclidine, 1.26g, (0.010 mole) in 10ml tetrahydrofuran was added dropwise to the stirred reaction mixture and stirring at room temperature continued for 3 hrs. TLC analysis (3% conc. ammonium hydroxide solution in methanol) showed some product formation. The mixture was heated at reflux temperature for 18 hours and then concentrated to an oil. TLC analysis showed the prsence of the product, imidazole, and 3-aminoquinuclidine. The oil was dissolved in methylene chloride (75ml) and washed twice with 50ml protions of aqueous sodium bicarbonate solution. The methylene chloride layer was dried over anhydrous magnesium sulphate and concentrated to yield 2.0g (67%) of a glassy amorphous solid, the free base of the title compound.

In another reaction on a 0.020 mole scale, 5.18g (83.8%) of the product as the free base was obtained.

The products were combined, dissolved in methanol (20ml) and the solution and treated with a solution of fumaric acid (2.73g) in methanol (50ml). Absolute ether was added to precipitate the salt which was collected by filtration and recrystallized from methanol-water (200:20) with isopropyl ether added to the point of incipient cloudiness. The recrystallized salt (5.38g) melted at 223-225 °C.

Analysis:	Calculated for $C_{19}H_{24}N_3O_6Cl$:	C,53.59;	H,5.68;	N,9.89
	Found :	C,53.35;	H,5.72;	N,9.95

From the racemate, the R(+) isomer and the S(-) isomer are separated.

EXAMPLE 2

R(+)-4-Amino-N-(1-azabicyclo[2.2.2]oct-3-yl)-5-chloro-2-methoxybenzamide, hydrochloride, hydrate (1.1.1).

(R(+)-4-Amino)-5-chloro-2-methoxy-N-(quinuclidin-3-ylbenzamide, hydrochloride, hydrate (1:1:1)).

To an isopropyl alcohol solution of the free base of the title compound such as was obtained by the procedure of Example 1 is added an equal molar amount of 37% (conc.) hydrochloric acid. The crude salt is separated by filtration and recrystallized from acetone-water to give the title compound, m.p. 158-160 °C. From the racemate, the R(+) isomer is separated.

EXAMPLE 3

R-N-(1-Azabicyclo[2.2.2]oct-3-yl)-5-chloro-2-methoxy-4-(methylamino)benzamide, fumarate [1:1].

(R-5-chloro-2-methoxy-4-methylamino-N-(quinuclidin-3-yl)benzamide, fumarate [1:1]).

To a mixture of 1,1′-carbonyldiimidazole, 1.23g (0. 00756 mole) and 5-chloro-2-methoxy-4-methylaminobenzoic acid, 1.63g (0.00756 mole) was added 50ml of tetrahydrofuran. Nitrogen was bubbled into the solution for 30 minutes to remove any carbon dioxide that was present. To the solution was added 3-aminoquinuclidine, 0.95g, (0.00756 mole) in one portion, and the reaction mixture was stirred at ambient temperature for 16 hours. The reaction mixture was concentrated to an oil which was shown to be 1:1 mixture of the free base of the product and imidazole. The mixture was dissolved in 20ml methanol and treated with a solution containing 0.47g fumaric acid in 20ml of hot methanol. Upon cooling, 1.52g of white

solid formed. Recrystallization from water-methanol gave 0.84g of the product as a white solid; m.p. 237-238 °C.

Analysis:	Calculated for $C_{20}H_{26}N_3O_6Cl$:	C,54.61;	H,5.96;	N,9.55
	Found :	C,54.61;	H,5.98;	N,9.51

From the racemate, the R isomer is separated.

EXAMPLE 4

R-N-(1-Azabicyclo[2.2.2]oct-3-yl)-5-chloro-2-methoxy-4-(methylamino)-benzamide, hydrochloride (1:1).

(R-5-chloro-2-methoxy-4-(methylamino)-N-(quinuclidin-3-yl)benzamide, hydrochloride (1:1).

To an isopropyl alcohol solution of the free base of the title compound, such as was obtained by the procedure of Example 3, is added an equal molar amount of 37% (conc.) hydrochloric acid. The crude salt is separated by filtration and recrystallized from ethanol-water to give the title compound, m.p. 255-258 °C. From the racemate, the R isomer is separated.

EXAMPLE 5

R-N-(1-Azabicyclo[2.2.2]oct-3-yl)-2-methoxybenzamide, fumarate [1.1]hemihydrate (R-2-methoxy-N-(quinuclidin-3-yl)benzamide, fumarate [1:1]hemihydrate)

In a closed system equipped with an oil bubbler, a solution of 2-methoxybenzoyl chloride, 2.76g (0.0016 mole) in 50ml absolute ether was added dropwise over 10 min to a stirred solution of 3-aminoquinuclidine, 1.81g (0.0144 mole) in 100ml absolute ether. After the addition was completed, the mixture was stirred at room temperature for an additional 2 hrs. The solid hydrochloride salt was collected by filtration under nitrogen. The salt (3.83g) was dissolved in sodium bicarbonate solution and extracted twice with 25ml portions of methylene chloride. The extract was dried over magnesium sulphate and concentrated to yield 1.25g clear oil (33.3%). TLC analysis (3% conc. ammonium hydroxide in methanol) showed the free base to be pure. A solution of 1.17g of the free base in 5ml methanol was treated with a solution of 0.52g fumaric acid in 10ml methanol. Isopropyl ether was added to give approximately 100ml of solution from which the fumarate salt precipitated. The salt was collected under nitrogen and dried in a vacuum oven at 60 °C overnight. NMR and elemental analyses showed that the product was a hemihydrate.

Analysis:	Calculated for $C_{19}H_{25}N_2O_{6.5}$:	C,59.21;	H,6.54;	N,7.27
	Found :	C,59.18;	H,6.30	N,7.25

From the racemate, the R isomer is separated.

EXAMPLE 6

R-N-(1-Azabicyclo[2.2.2]oct-3-yl)-2,4-dimethoxy-benzamide hydrochloride [1:1].

(R-N-(quinuclidinyl-3-yl)-2,4-dimethoxybenzamide hydrochloride [1:1]

A mixture of 3-aminoquinuclidine dihydrochloride, 6.95g, (0.0349), 2,4-dimethoxybenzoyl chloride, 700g, (0.0349 mole), anhydrous sodium carbonate, 36.99g, (0.349 mile), 175ml water, and 175ml chloroform was stirred rapidly to achieve good mixing of the 2 layers for 20 hrs. The chloroform layer was then separated, washed with water, dried over anhydrous magnesium sulphate, and concentrated to an impure oil. The oil was triturated twice with 20ml portions of petroleum ether to remove some impurities. The oil was then dissolved in ether and filtered to remove a small amount of insoluble material. The filtrate was treated with ethereal hydrogen chloride and the resulting salt collected to yield 2.70g (23.7% yield) white solid. The salt was recrystallized from ethanol-isopropyl ether. Further recrystallization from methanol-ethyl ether yielded a white solid, m.p. 211-212° C. The NMR analysis was satisfactory.

Analysis:	Calculated for $C_{16}H_{23}N_2O_3Cl$:	C,58.80;	H,7.09;	N,8.57
	Found :	C,58.38;	H,7.13;	N,8.44

From the racemate, the R isomer is separated.

EXAMPLE 7

R-N-(1-Azabicyclo[2.2.2]oct-3-yl)-2,4-dimethoxybenzamide, sulphate[1:].

(R-2,4-dimethoxy-N-(quinuclidin-3-yl)benzamide, sulphate[1:]).

In a closed system equipped with an oil bubbler, a solution of 2,4-dimethoxybenzoyl chloride, 13.08g, (0.0652 mole) in 200ml absolute ether was added dropwise over 30 minutes to a stirred solution of 3-aminoquinuclidines 7.80g, (0.0619 mole) in 200ml absolute ether. The mixture was stirred overnight, and the solid hydrochloride salt of the product was filtered under nitrogen. The material was dried in a vacuum oven at 40° C to give 18.70g (92%). A 2.94g (0.009 mole) portion of the hydrochloride salt in 20ml methanol was treated with a solution of sodium methoxide prepared from 0.23g (0.010 mole) sodium metal and 10ml methanol. After standing a few minutes, the mixture was filtered and the filtrate concentrated on a rotary evaporator, and the residue was triturated with 75ml methylene chloride. After filtering to remove some insoluble solids, the filtrate was concentrated to yield 2.53g of the free base of the title compound (97% recovery from the hydrochloride salt). The free base was dissolved in 100ml acetone and concentrated sulphuric acid (0.483ml) added dropwise with stirring. The solid that formed was collected under nitrogen to give 2.76g of the salt which recrystallized from methanol-isopropyl ether and dried in a vacuum oven at 60° C for 2 hrs and then overnight at 78° C; m.p. 223-225° C.

Analysis:	Calculated for $C_{16}H_{24}N_2O_7S$:	C,49.47;	H,6.23;	N,7.23
	Found :	C,49.41;	H,6.30;	N,7.25

From the racemate, the R isomer is separated.

EXAMPLE 8

R-N-(1-Azabicyclo[2.2.2]oct-3-yl)-2,4-dimethoxybenzamide, fumarate [1:1.5].

(R-2,4-dimethoxy-N-(quinuclidin-3-yl)benzamide, fumarate [1:1.5]).

In a closed system equipped with an oil bubbler, tetrahydrofuran, 100ml, was added to a mixture of 2,4-dimethoxybenzoic acid, 3.64g (0.020 mole) and 1,1′-carbonyldiimidazole, 3.24g (0.020 mole). No evolution of carbon dioxide was observed and after stirring for 3 hrs, TLC (ethyl acetate) and mass spectral analysis showed that the starting material had reacted to form N-(2,4-dimethoxybenzoyl)imidazole and imidazole. A solution of 3-aminoquinuclidine, 2.52g (0.020 mole) in 10ml tetrahydrofuran was added to the mixture, and the solution was heated to reflux temperature for 1 hr and then allowed to stand overnight at room temperature. A solution of fumaric acid, 2.32g (0.020 mole) in 50ml methanol was added to the reaction mixture. Tetrahydrofuran was added until the solution became slightly turbid. The solution was chilled in a refrigerator. The solid which precipitated from solution was collected by filtration and found to be a fumarate salt of 3-aminoquinuclidine. The filtrate was concentrated to an oil and triturated with tetrahydrofuran. The solid precipitate which formed on standing was filtered and shown by TLC (3% concentrated ammonium hydroxide in methanol) to be the desired product plus traces of imidazole and 3-aminoquinuclidine. Recrystallization from methanol-isopropyl ether gave 5.41g white crystalline solid (67% yield calculated as the monofumarate). NMR and elemental analysis showed the salt to contain less than one equivalent of fumaric acid. The salt was dissolved in boiling methanol (50ml) and treated with an additional 0.77g (0.0066 mole) fumaric acid in 10ml hot methanol. Isopropyl ether was added until the hot solution became turbid. The solid obtained on cooling was collected, recrystallized from methanol-isopropyl ether and dried in a vacuum oven at 78° C overnight. NMR and elemental analysis showed the salt to be a 1.5 fumarate, m.p. 192.192.5° C.

Analysis:	Calculated for $C_{22}H_{28}N_2O_9$:	C,56.89;	H,6.08;	N,6.03
	Found :	C,56.81;	H,6.13;	N,6.04

From the racemate, the R isomer is separated.

EXAMPLE 9

R-N-(1-Azabicyclo[2.2.2]oct-3-yl)-2-propoxybenzamide hydrochloride [1:1].

(R-2-propoxy-N-(quinuculidin-3-yl)benzamide hydrochloride [1:1])

To a solution of 3.82g (0.0192 mole) of 3-amino-quinuclidine dihydrochloride in about 25ml of carbon dioxide-free water was added 8g (0.025 mole) of barium hydroxide octahydrate. The mixture was warmed for 5 minutes and then dried to a powder on a rotary evaporator. While protecting from contamination with carbon dioxide in the atmosphere, the powder was extracted in sequence with hot benzene and a 1:1 mixture of benzene-methylene chloride solution. The combined extracts were dried over magnesium sulphate and the mixture filtered. To the filtrate with agitation was added dropwise a solution of 3.4g (0.0171 mole) 2-propoxybenzoyl chloride in 50ml of methylene chloride. The mixture was warmed on a steam bath to evaporate about 75% of the methylene chloride. Ligroin (60-110) was added and the mixture solidified. The solid was recrystallized from anhydrous ethyl alcohol to give 3.9g (62.0%), m.p. 210-211° C.

Analysis:	Calculated for $C_{17}H_{25}N_2O_2Cl$:	C,62.86;	H,7.75;	N,8.62
	Found :	C,62.62;	H,7.59;	N,8.54

From the racemate, the R isomer is separated.

EXAMPLE 10

R-N-(1-Azabicyclo[2.2.2]oct-3-yl)-3-methoxy-2-naphthalene-carboxamide hydrochloride [1:1]

(R-3-methoxy-2-naphthalene-N-(quinuclidin-3-yl)carboxamide, hydrochloride [1:1]).

A solution of 1.69g (0.00768 mole) of 3-methoxy-2-naphthoic acid chloride in 15ml of methylene chloride was added dropwise to a stirred solution of 0.97g (0.00768 mole) of 3-aminoquinuclidine in 25ml of methylene chloride in a closed system equipped with an oil bubbler. The reaction mixture was stirred overnight at ambient temperature, and then concentrated to give an off-white glassy solid. Two recrystallizations from methanol-isopropyl ether gave 1.95g (73.4%) of the product as an off-white solid which was vacuum dried at ambient temperature, m.p. 248-252 °C.

analysis: Calculated for $C_{19}H_{23}N_2O_2Cl$: C,65.79; H,6.68; N,8.08

Found : C,65.40; H,6.72; N,8.01

From the racemate, the R isomer is separated.

EXAMPLE 11

R-4-Amino-N-(1-azabicyclo[2.2.2]oct-3-yl)-5-chloro-2-methoxythiobenzamide fumarate.

(R-4-Amino-5-chloro-2-methoxy-N-(quinuclidin-3-yl)thiobenzamide fumarate).

One half mole of 4-amino-N-(1-azabicyclo[2.2.2]oct-3-yl)-5-chloro-2-methoxybenzamide fumarate is partitioned between dilute sodium hydroxide and 400ml of benzene. The benzene solution is dried with sodium sulphate and distilled to a volume of 250ml. To this is added a finely-ground mixture of 9g of phosphorous pentasulphide and 9g of potassium sulphide. The mixture is refluxed for 4 hr and an additional 9g of phosphorous pentasulphide is added and reflux continued for 2 hr. The benzene is decanted off. The solid is dissolved in a suitable solvent and reacted with fumaric acid to give the title compound. From the racemate the 3-R isomers are separated.

EXAMPLE 12

R-4-Amino-N-(1-aza-2-methylbicyclo[2.2.2]oct-3-yl)-5-chloro-2-methoxybenzamide fumarate [1:1]

(R-4-Amino-5-chloro-2-methoxy-N-(2-methylquinuclidin-3-yl)benzamide, fumarate [1:1])

Following the general procedure of Example 1, but instead of the 3-aminoquinuclidine, using 0.010 moles , of 3-amino-2-methylquinuclidine, the title compound was prepared. From the racemate, the 3-R isomers were separated.

EXAMPLE 13

R-4-Amino-N-(1-aza-2-methylbicyclo[2.2.2]oct-3-yl)-5-chloro-2-methoxybenzamide, hydrochloride, hydrate (1:1:1)

R-4-Amino-5-chloro-2-methoxy-N-(2-methylquinuclidin-3-yl)benzamide, hydrochloride, hydrate (1:1:1)

To an isopropyl alcohol solution of the free base of the title compound such as was obtained by the procedure of Example 1 is added an equal molar amount of 37% (conc.) hydrochloric acid. The crude salt is separated by filtration and recrystallised from acetone-water to give the title compound. From the racemate, the 3-R isomers were separated.

PREPARATION 1

R(+)-3-aminoquinuclidine, dihydrochloride

(R(+)-1-azabicyclo[2.2.2]oct-3-ylamine dihydrochloride)

(a) Preparation of R(+)-N-(3-quinuclidinyl)-3-chlorobenzamide, hydrochloride R(+)-N-(1-azabicyclo[2.2.2[]-oct-3-yl)-5-chloro-2-methoxybenzamide, hydrochloride)

N-(3-quinuclidinyl)-3-chlorobenzamide (52.5 g) in solution in methanol is added to a solution of L-tartaric acid (29.7 g) in methanol. The precipitate obtained is recovered by filtration and treated twice with methanol at reflux. The salt thus purified is decomposed by an aqueous caustic soda solution and the product extracted with chloroform. After drying and evaporation of the organic phase the base obtained is treated in acetone with an ethanolic hydrochloric acid solution. The hydrochloride which precipitates is recovered by filtration and recrystallised from ethanol. 9.4 g of optically pure R(+)-N-(3-quinuclidinyl)-3-chlorobenzamide, hydrochloride (R(+)-N-(1-azabicyclo[2.2.2]oct-3-yl)-5-chloro-2-methoxy-benzamide, hydrochloride) are obtained. Melting point: 244° - 247° C.
$[\text{alpha}]_D^{20}$ = +16.9° (1, CH_3OH)

(b) Preparation of R(+)-3-aminoquinuclidine, dihydrochloride (R(+)-1-azabicyclo[2.2.2]oct-3-ylamine, dihydrochloride)

The hydrochloride obtained in the preceding step (9 g) is treated with concentrated hydrochloric acid at reflux for 3 hours 30 minutes. The reaction mixture is treated with absolute alcohol and the R(+)-3-aminoquinuclidine, dihydrochloride (R(+)-1-azabicyclo[2.2.2] oct-3 -ylamine, dihydrochloride) which crystallises is recovered by filtration. Melting point: >260° C
$[\text{alpha}]_D^{20}$ = +24.8° (c=1, H_2O)

PREPARATION 2

R(+)-3-aminoquinuclidine, dihydrochloride

(R(+)-1-azabicyclo[2.2.2]oct-3-ylamine dihydrochloride)

(a) Preparation of S(-)-N-(alpha-methylbenzyl)-3- quinuclidinimine

3-Quinuclidinone (80 g) in 800 ml toluene was refluxed in the presence of S-alpha-methylbenzylamine (77.4 g) for 24 hours, the water formed being eliminated by means of a Dean-Stark trap. The reaction mixture is then concentrated to dryness and the resulting imine (130 g) is distilled. Yield: 89%
Boiling point: 140° - 150° C (0.05 mm Hg)
$[\text{alpha}]_D^{20}$ = -98.6° (c=1, $CHCl_3$)

(b) Preparation of S-N-(alpha-methylbenzyl)-R-3-aminoquinuclidine, dihydrochloride

The imine (129.5 g) obtained in the preceding step is dissolved in methanol and potassium borohydride (30.6 g) is added in small portions at between 10° and 20° C. After one hour the mixture is evaporated to dryness under reduced pressure. The residue is dissolved in a mixture of acetone and isopropyl alcohol (2:1). The expected amine is precipitated in the form of the dihydrochloride by the addition of an ethanolic hydrogen chloride solution. The product is recrystallised twice in an ethanol/methanol mixture (1:1) to yield optically pure S-N-(alpha-methylbenzyl)R-3-aminoquinuclidine, dihydrochloride (81 g). Yield: 47%
Melting point >260° C
$[\text{alpha}]_D^{20}$ = +1.8 (2, H_2O)

(c) Preparation of R(+)-3-aminoquinuclidine, dihydrochloride (R(+)-1-azabicyclo[2.2.2]oct-3-ylamine, dihydrochloride)

The product obtained in the preceding step (64.4 g) is dissolved in ethanol with 2 equivalents of a solution of hydrochloric acid (1 N) and palladium on carbon, 50% H_2O (12.8 g). The reaction mixture is stirred for 18 hours under a hydrogen atmosphere, filtered then evaporated to dryness under reduced pressure. R(+)-3-aminoquinuclidine, dihydrochloride is crystallised in an ethanol:ether (1:1) mixture. $[\text{alpha}]_D^{20}$ = +24.4 (1, H_2O)

PREPARATION 3

R(+)-3-aminoquinuclidine, dihydrochloride

(R(+)-1-azabicyclo[2.2.2]oct-3-ylamine, dihydrochloride)

(a) R(-)-3-phthalimidoquinuclidine

S(+)-3-quinuclidinol (13.4 g: 0.105 mole), triphenyl phosphine (30.4 g: 0.115 mole) and phthalimide (15.7 g: 0.106 mole) are suspended in anhydrous THF (100 ml) at 0° C. Ethyl azodicarboxylate (17.7 ml: 0.115 mole) is added. After returning to ambient temperature, the solution is agitated for 2 hours. The solvent is evaporated, the reaction mixture taken up in ethyl acetate and the organic phase is extracted by an aqueous solution of hydrochloric acid (1 N). After washing with ethyl acetate, the aqueous phase is neutralised with $NaHCO_3$ and the product is extracted with chloroform. After drying and evaporation of the organic phase, the residue is crystallised in a mixture of petroleum ether and isopropyl ether, to give 19.3 g (72%) R-3-phthalimidoquinuclidine.

(b) R(+)-3-aminoquinuclidine, dihydrochloride (R(+)-1-azabicyclo[2.2.2]oct-3-ylamine, dihydrochloride)

The phthalimide obtained in step (a) (14.5 g: 0.056 mole) is refluxed in 200 ml ethanol in the presence of hydrazine hydrate (3.1 g: 0.062 mole) for 1 hour 30 minutes. Insoluble matter is removed by filtration and the ethanol is removed under vacuum. The residue is taken up in diethyl ether and the fresh insoluble matter eliminated by filtration. After evaporation of the ether, R(+)-3-aminoquinuclidine dihydrochloride (10.5 g: 72%) is crystallised by a solution of hydrochloric acid in ethanol. Melting point: >260°C
$[\text{alpha}]_D^{20}$ = +24.4 (c=1, H_2O)

COMPARISON PREPARATION 1

S(-)-3-aminoquinuclidine, dihydrochloride (S(-)-1-azabicyclo[2.2.2]oct-3-ylamine dihydrochloride)

Following the procedure of Preparation 1, but using instead D-tartaric acid, the corresponding S enantiomer was obtained. Melting point: >260°C $[\text{alpha}]_D^{20}$ = -24.9° (c=1, H_2O)

COMPARISON PREPARATION 2

S(-)-3-aminoquinuclidine, dihydrochloride (S(-)-1-azabicyclo[2.2.2]oct-3-ylamine, dihydrochloride)

Following the procedure of Preparation 2, but using instead R-N-alpha-methylbenzylamine, the corresponding S enantiomer was obtained. Melting point: >260°C
$[\text{alpha}]_D^{20}$ = -24.2° (c=1, H_2O)

EXAMPLE 14

R(+)-4-Amino-N-(3-quinuclidinyl)-5-chloro-2-methoxybenzamide hydrochloride

(R(+)-4-Amino-N-(1-azabicyclo[2.2.2]oct-3-yl)-5-chloro2-methoxybenzamide hydrochloride)

R(+)-3-aminoquinuclidine dihydrochloride (40 g: 0.2 mole) is dissolved in an aqueous caustic soda solution (2.5 N). To this solution, cooled in an ice bath, is added 4-amino-5-chloro-2-methoxy benzoic acid (44.5 g) in solution in 300 ml of pyridine. Dicyclohexylcarbodiimide (85 g) is added in two portions. The mixture is vigorously stirred for 18 hours at ambient temperature. The medium is then diluted with 150 ml of water. Insoluble matter is removed by filtration and washed with water. The aqueous phase is brought to pH 10 by a 10 N solution of caustic soda and extracted by chloroform. After drying (over Na_2SO_4) and evaporation of the organic phase, the residue is crystallised in isopropyl ether.

The solid thus obtained (56 g) is dissolved in 280 ml isopropyl alcohol and the solution acidified by 5 N HCl. The hydrochloride which precipitates is recovered by filtration and recrystallised in 99% ethanol. The target product is obtained with a yield of 60%. Melting point: 232-234°C
$[\text{alpha}]_D^{20}$ = +3.8° (c=1, H_2O)

COMPARISON EXAMPLE 1

S(-)-4-Amino-N-(3-quinuclidinyl)-5-chloro-2-methoxy-benzamide hydrochloride

(S(-)-4-Amino-N-(azabicyclo[2.2.2]oct-3-yl)-5-chloro-2-methoxybenzamide hydrochloride)

Following the procedure of Example 14 but using instead S(-)-3-aminoquinuclidine as prepared in Comparison Preparation 1 or 2, the corresponding S enantiomer is obtained. Melting point: 233-235 °C
[alpha]$_D^{20}$ = -3.9° (c = 1, H_2O)

EXAMPLE 15

R(+)-4-Amino-N-(3-quinuclidinyl)-5-chloro-2-methoxy-benzamide hydrochloride

(R(+)-4-Amino-N-(1-azabicyclo[2.2.2]oct-3-yl)-5-chloro-2-methoxybenzamide hydrochloride)

R(+)-3-aminoquinuclidine (1.9 g) is dissolved in 33.5 ml of an aqueous 1 N caustic soda solution. To this solution is added drop by drop 4-acetamido-5-chloro-2-methoxybenzoyl chloride (3.75 g) in solution in 70 ml dioxane. After 15 minutes stirring, the reaction medium is acidified, washed with chloroform, basified with a concentrated aqueous caustic soda solution and the product extracted with chloroform. The organic phase is dried (over sodium sulphate) and then evaporated. The oily residue is dissolved in ethanol and ethanol/HCl is added to an acid pH. The 4-acetamido-5-chloro-2-methoxy-N-(3-quinuclidinyl)-benzamide hydrochloride so formed precipitates (quantitative yield) and is recovered by filtration.
The product is subsequently deacylated by refluxing for 30 minutes in a 5% solution of potassium hydroxide in ethanol. The reaction medium is then dissolved in water and extracted with chloroform. After drying and evaporation of the organic phase, the target hydrochloride is prepared and isolated as described in Example 14. Melting point: 232-234 °C
[alpha]$_D^{20}$ = +3.8° (c = 1, H_2O)

COMPARISON EXAMPLE 2

S(-)-4-Amino-N-(3-quinuclidinyl)-5-chloro-2-methoxybenzamide dihydrochloride

(S(-)-4-Amino-N-(1-azabicyclo[2.2.2]oct-3-yl)-5-chloro-2-methoxybenzamide dihydrochloride)

Following the procedure of Example 15 but using instead S(-)-3-aminoquinuclidine as prepared in Comparison Preparation 1 or 2, the corresponding S enantiomer is obtained. Melting point: 233-235 °C
sulphate$_D^{20}$ = -3.9° (c = 1, H_2O)

EXAMPLE 16

R(+)-N-(3-quinuclidinyl)benzamide hydrochloride (R(+)-N-(1-azabicyclo[2.2.2]oct-3-yl)benzamide hydro-

chloride)

Following the procedure of Example 14 but using benzoic acid in place of the 4-amino-5-chloro-2-methoxybenzoic acid, the title compound was prepared. Melting point: 245° C
$[alpha]_D^{20}$ = +17.8(1, CH_3OH)

EXAMPLE 17

R(+)-N-(3-quinuclidinyl)benzamide hydrochloride (R(+)-N-(1-azabicyclo[2.2.2]oct-3-yl)benzamide hydrochloride)

Following the procedure of Example 15 but using benzoyl chloride in place of the 4-amino-5-chloro-2-methoxybenzoyl chloride, the title compound was prepared. Melting point: 245° C
$[alpha]_D^{20}$ = +17.8(1, CH_3OH)

EXAMPLE 18

R(+)-3-chloro-N-(3-quinuclidinyl)benzamide hydrochloride

(R(+)-N-(1-azabicyclo[2.2.2]oct-3-yl)-3-chlorobenzamide hydrochloride)

Following the procedure of Example 14 but using 3-chlorobenzoic acid in place of the 4-amino-5-chloro-2-methoxybenzoic acid, the title compound was prepared. Melting point: 244° C
$[alpha]_D^{20}$ = +16.9 (1, CH_3OH)

EXAMPLE 19

R(+)-3-chloro-N-13 quinuclidinyl)benzamide hydrochloride

(R(+)-N-(azabicyclo[2.2.2]oct-3-yl)-3-chlorobenzamide hydrochloride)

Following the procedure of Example 15 but using 3-chlorobenzoyl chloride in place of the 4-amino-5-chloro-2-methoxybenzoyl chloride, the title compound was prepared. Melting point: 244° C
$[alpha]_D^{20}$ = +16.9(1, CH_3OH)

EXAMPLE 20

R(+)-4-chloro-N-(3-quinuclidinyl)benzamide hydrochloride

(R(+)-N-(1-azabicyclo[2.2.2]oct-3-yl)-4-chlorobenzamide hydrochloride)

Following the procedure of Example 14 but using 4-chlorobenzoic acid in place of the 4-amino-5-chloro-2-2-methoxybenzoic acid, the title compound was prepared. Melting point: >260 °C
$[\alpha]_D^{20}$ = +12.5 (1, CH_3OH)

EXAMPLE 21

R(+)-4-chloro-N-(3-quinuclidinyl)benzamide hydrochloride

(R(+)-N-(azabicyclo[2.2.2]oct-3-yl)-4-chlorobenzamide hydrochloride)

Following the procedure of Example 15 but using 4- chlorobenzoyl chloride in place of the 4-amino-5-chloro-2-methoxybenzoyl chloride, the title compound was prepared. Melting point: >260 °C
$[\alpha]_D^{20}$ = +12.5 (1, CH_3OH)

EXAMPLE 22

R(+)-3,5-dichloro-N-(3-quinuclidinyl)benzamide hydrochloride

(R(+)-N-(1-azabicyclo[2.2.21oct-3-yl)-3,5-dichlorobenzamide hydrochloride)

Following the procedure of Example 14 but using 3,5-dichlorobenzoic acid in place of the 4-amino-5-chloro-2-methoxybenzoic acid, the title compound was prepared. Melting point: >260 °C
$[\alpha]_D^{20}$ = +14.1 (1, CH_3OH)

EXAMPLE 23

R(+)-3,5-dichloro-N-(3-quinuclidinyl)benzamide hydro-chloride

(R(+)-N-(1-azabicyclo[2.2.2]oct-3-yl)-3,5-dichlorobenzamide hydrochloride)

Following the procedure of Example 15 but using 3,5-dichlorobenzoyl chloride in place of the 4-amino-5-chloro-2-methoxybenzoyl chloride, the title compound was prepared. Melting point: >260 °C
$[\alpha]_D^{20}$ = +14.1 (1, CH_3OH)

PHARMACOLOGY EXAMPLE

A simple test was used which allows mice to move from an aversive environment. The test system essentially comprises a box separated into a white, brightly-lit compartment, and a black, dimly lit compartment, the two being separated by a partition with access between the two enabled by an opening at floor level in the partition. Mice taken from the dark and placed in the centre of the white, brightly-lit

compartment find this aversive, and will move around the perimeter of the area until access to the dark environment is located and appreciated. On repeated exposure to the test situation mice 'learn' rapidly to locate the access to the black area and to spend the majority of test time in the black where most exploratory behaviour is exhibited. Habituation to the test system occurs over several days.

Methods

The studies used male albino (BKW) mice initially weighing 25-30g. In their home room mice were housed in groups of 10 and were given free access to food and water. The mice were kept on a 12h light and 12h dark cycle with lights off at 8.00am and on at 8.00pm.

The test apparatus consisted of an open-topped box (45 x 27 x 27cm) two-fifths painted black and illuminated under a dim red light (1 x 60W) and partitioned from the remainder of the box which was brightly illuminated with a 100W light source located 17cm above the box. Access between these two areas was enabled by means of a 7.5 x 7.5cm opening located at floor level in the ce tre of the partition (which also served to prevent diffusion of light between the two compartments of the test box). The floor area was lined into 9cm squares.

The habituation test was carried out daily by placing mice in the centre of the white section of the test box (mice taken from dark home environment in a dark container, to the experimental room maintained in low red lighting, and would normally be averse to the bright white conditions). Testing was carried out between 8.30am and 12.30pm. The test period was 5min per day. Behaviour was assessed via remote video recording, and the following measures taken:

1. Latency to move from the white to the black section (sec).
2. Numbers of exploratory rears in the white and black sections during the 5min test.
3. Numbers of line crossings (exploratory locomotion) in the white and black sections during the 5min test.
4. % time spent in the black section of the box during the 5min test.
5. Numbers of transitions between the black and white sections of the test box during the 5min test (since this parameter was not changed in any situation in the present studies, data for transitions is not given or commented on further).

Generally, as animals habituated to the test system they would move quickly into the black section of the box where most behavioural exploration was exhibited, and measured as numbers of exploratory rears and line crossings.

Habituation was disrupted by a single challenge with scopolamine 30min before test. the dose (0.25mg/kg) was carefully selected as being minimally effective, without interference from peripheral effects as checked by assessment of the actions of the same dose of methylscopolamine.

The doses of compounds under test were carefully selected as being just subanxiolytic (an anxiolytic action, exhibited as reduced aversion for the white area of the test box, would interfere with the measurement of habituation). Racemic 4-amino-N-(1-azabicyclo[2.2.2]oct-3-yl)-5-chloro-2-methoxybenzamide hydrochloride (ie the racemate of the R(+) enantiomer of Example 14 improved performance in the habituation test, and antagonised the impairment caused by scopolamine, at a dose of 100mg/kg i.p. b.d. The compound of Example 14 itself, R(+)-4-amino-N-(1azabicyclo[2.2.2]oct-3-yl)-5-chloro-2-methoxybenzamide hydrochloride, was used at a dose of 10nk/kg i.p. b.d. (a dose of 50ng/kg i.p. b.d. was anxiolytic), and the compound of Comparison Example 1 (the corresponding S enantiomer) at 50ng/kg i.p. b.d. (inactive as an anxiolytic at low to moderate dosage). All drugs were prepared in normal saline and administered in a volume of 1ml/100g body weight. Doses were calculated as base.

Results

The results are described with reference to the accompanying figures, in which:

Figure 1 shows the effect of compounds under test in reducing the latency (measured in seconds) for mice moving from the black compartment to the white compartment; this learned response was impaired on day 6 by the administration of scopolamine, 0.25 mg/kg i.p;

Figure 2 shows the effects of the compounds under test in increasing the time spent in the black section of the box;

Figure 3 shows the effects of the compounds under test on the mice learning to avoid the white, averse environment and exhibit most behaviour in the black, shown here as reduced rearing behaviour in

the white (hatched columns) with corresponding increased rearing behaviour in the black (stippled columns); and

Figure 4 again shows the effects of the compounds under test on the mice learning to avoid the white, averse environment and exhibit most behaviour in the black, shown here as reduced exploratory line crossings in the white (hatched columns) with corresponding increased exploratory line crossings in the black (stippled columns).

Mice allowed to habituate to the black:white test box environment learn within 3-4 days that a less aversive black environment is available when they pass through the partition from the bright white environment. Latency to move from the white to the black environment progressively decreases over a 5 day period, and for many animals an initial latency of 11-13sec is reduced to 1-3sec (see Fig. 1). In Figs. 1 to 4, the symbols shown have the following significance:

* facilitation of learning

+ impairment of learning

x scopolamine impairment

o antagonism of scopolamine impairment

and the following statistical data apply:

(Fig 1)	n = 6-7 SEMs <12.3% P<0.05-P<0.001 (Dunnett's t test)
(Fig 2)	n = 6-7 SEMs <13.0% P<0.05-P<0.001 (Dunnett's t test)
(Fig 3)	n = 6-7 SEMs <12.1% P<0.05-P<0.001 (Dunnett's t test)
(Fig 4)	n = 6-7 SEMs <12.6% P<0.05-P<0.001 (Dunnett's t test)

Animals thus spend progressively less time in the white compartment, and more time the black, dimly lit area of the box, and this is reflected not only in measurements of % time spent in the black compartment, but also as an increase in exploratory behaviour in the black (rearing behaviour, exploratory locomotion measured as crossings of lines marked on the cage floor) and decreased exploratory behaviour in the white (Figs. 3 and 4).

The speed of acquisition of habituation was enhanced by the compound of Example 14 (R isomer). Latency to move from the white to the black compartment was significantly decreased below control values between days 2-4 (habituation maximum in control animals by day 5 and no further improvement is measurable) (Fig. 1), and there were corresponding increases above control values of time spent in the black (significant on day 2, see Fig. 2), with decreases in activity (rearings and line crossings) in the white and corresponding increases in these behaviours in the black (significant on days 2-4, see Figs. 3 and 4).

In contrast to the actions of the compound of Example 14, the compound of Comparison Example 1 (the corresponding S-enantiomer) did not improve performance in the habituation test on any day of testing. Indeed, in contrast, impairment in acquisition of habituation was significant on days 3-5 (on measure of latency, Fig. 1 and on days 4-5 (on measures of rearings and line crossings, Figs. 3 and 4).

A single challenge with scopolamine was shown to impair habituation performance, seen as delayed latency (Fig. 1), reduced % of time in black (Fig. 2), and increased exploratory behaviour in the white (Figs. 3 and 4) (i.e. animals no longer appear able to perform the behavioural repertoire to effect avoidance of the averse environment). This impairment caused by scopolamine was completely prevented in those animals which had received continued treatment with the compound of Example 14 but was not modified by treatments with the compound of Comparison Example 1 (Figs. 1-4).

This example therefore shows that improved performance in the habituation test, and antagonism of scopolamine impairment, is achieved by the compound of Example 14, the R isomer. In contrast, the compound of Comparison Example 1, the S isomer, failed to improve performance in the habituation test

and failed to antagonise the impairment caused by scopolamine. Indeed, the performance of mice in the habituation test was, dependent on the time and measure, impaired by the S isomer of zacopride.

Pharmaceutical Methods and Compositions

Generally, learning and/or memory can be enhanced by means of this invention by administering internally to warm blooded animals including human beings certain R(+)-N-(1-azabicyclo[2.2.2]oct-3-yl)-benzamides and thiobenzamides of Formula I, preferably Formula Ic, or a non-toxic organic or inorganic acid addition salt thereof in a wide variety of pharmaceutical forms well known in the art, preferably with a non-toxic pharmaceutical carrier such as is described below in an amount to enhance memory and/or learning.

The active agent is administering orally, subcutaneously, intravenously or intramuscularly or parenterally and, if necessary, in repeated doses until satisfactory response is obtained. The daily dosage is from about 0.2 mcg to about 10 mg of active medication, advantageously from about 1 mcg to 1.0 mg.

The compositions may contain 0.2 mcg to 10 mg active medicament per unit dose. Preferably, the compositions contain from about mcg to 10 mg of medicament, advantageously from about 1 mcg to about 1.0 mg per unit dose. The compounds may thus be presented in a therapeutic composition suitable for oral, parenteral, subcutaneous, intramuscular, intraperitoneal or intravenous administration. Thus, for example oral administration can take the form of elixirs, capsules, tablets or coated tablets containing carriers conveniently used in the pharmaceutical art. Exemplary of solid carriers including tableting and capsulating excipients are lactose, sucrose, potato and maize starches, talc, gelatin, agar, pectin or acacia; stearic and silicic acids, magnesium stearate, terra alba and polyvinyl pyrrolidone.

For parenteral administration, the carrier or excipient can be comprised of a sterile parenterally acceptable liquid; e.g., water or arachis oil contained in ampoules.

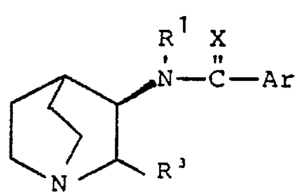
The pharmaceutical compositions may be formulated to contain from about 0.2 mcg/ml to about 10.0 mg/ml, preferably 10 mcg/ml or less. It is only necessary that the active ingredient of Formula I constitute an effective amount.

In all of the above, it is only necessary that a suitable effective dosage will be consistent with the dosage form employed. The exact individual dosages, as well as daily dosages, will of course be determined according to standard medical principles under the direction of a physician or veterinarian.

The principles, preferred embodiments and modes of operation of the present invention have been described in the foregoing specification. The invention which is intended to be protected herein, however, is not to be construed as limited to the particular forms disclosed, since these are to be regarded as illustrative rather than restrictive. Variations and changes may be made by those skilled in the art without departing from the spirit of the invention, and it is therefore understood that the invention is to be limited only by the scope of the appended claims.

Claims

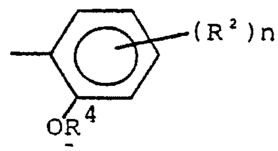
1. The use of a compound of general formula I



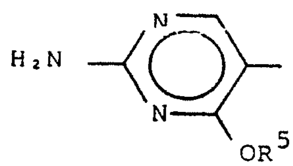
(I)

wherein:
X represents oxygen or sulphur;
each of R^1 and R^3 independently represents hydrogen or a C_1-C_4 alkyl group;
Ar represents:

a phenyl ring optionally substituted by one, two or three C_1-C_4 alkoxy groups and/or by one or two halogen atoms;
a phenyl ring of the general formula



wherein R^2 represents halogen, 4,5-benzo, C_1-C_8 alkoxy, C_1-C_4 alkylcarbonyl or Am, wherein Am represents amino, methylamino or dimethylamino,
R^4 represents C_1-C_8 alkyl,
n is 1 or 2; or
a pyrimidinyl moiety of the general formula



wherein R^5 is C_1-C_4 alkyl;
or an N-oxide and/or pharmaceutically acceptable salt thereof
in the preparation of an agent for enhancinglearning or memory.

2. The use as claimed in claim 1, wherein each of R^1 and R^3 independently represents hydrogen, methyl or ethyl.

3. The use as claimed in claim 1 or 2, wherein Ar represents 4-Am-5-chloro-2-methoxyphenyl.

4. The use of R-(+)-4-amino-N-(1-azabicyclo[2.2.2]oct-3-yl)-5-chloro-2-methoxybenzamide or a salt thereof in the preparation of an agent for enhancinglearning or memory.

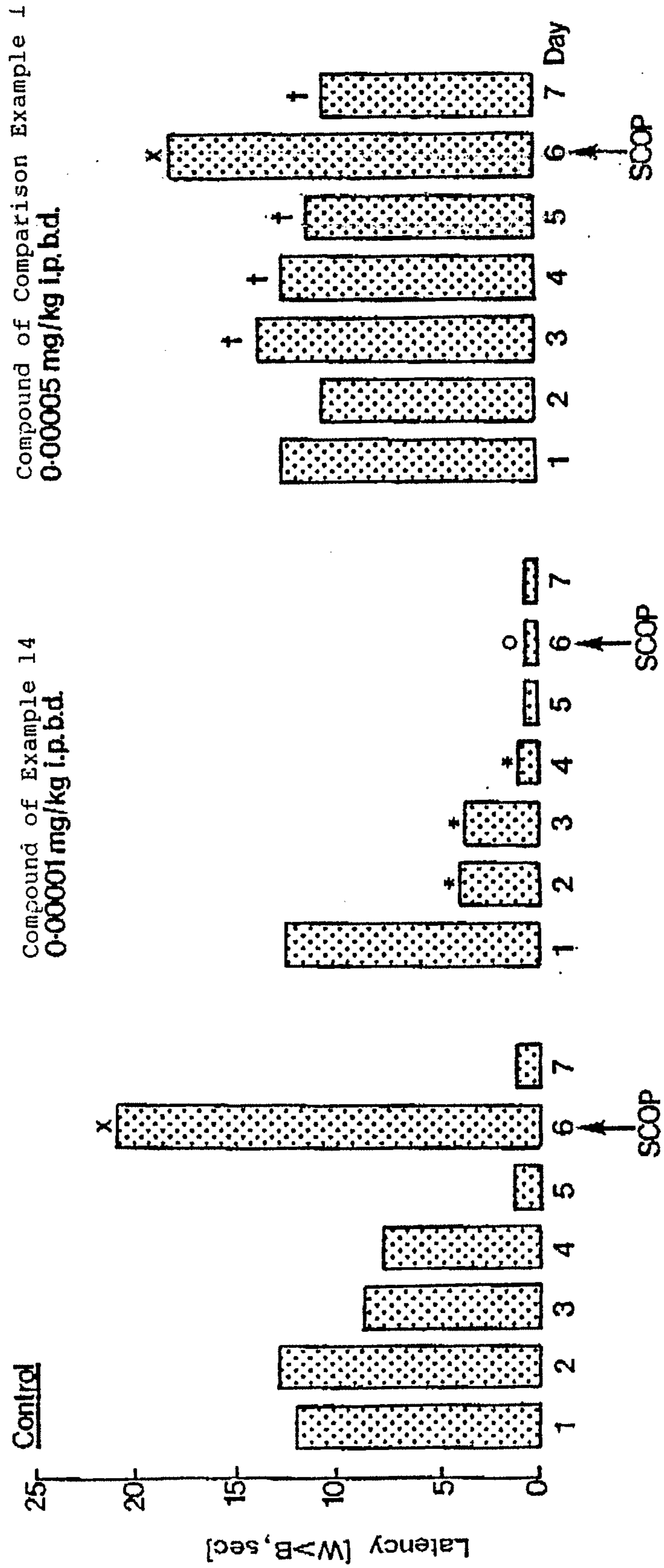

Latency [W>B, sec]
0
5
10
15
20
25
Control
Compound of Example 14
0·00001 mg/kg i.p.b.d.
Compound of Comparison Example 1
0·00005 mg/kg i.p.b.d.
1
2
3
4
5
6
7
Day
SCOP
x
*
o
+

FIGURE 1

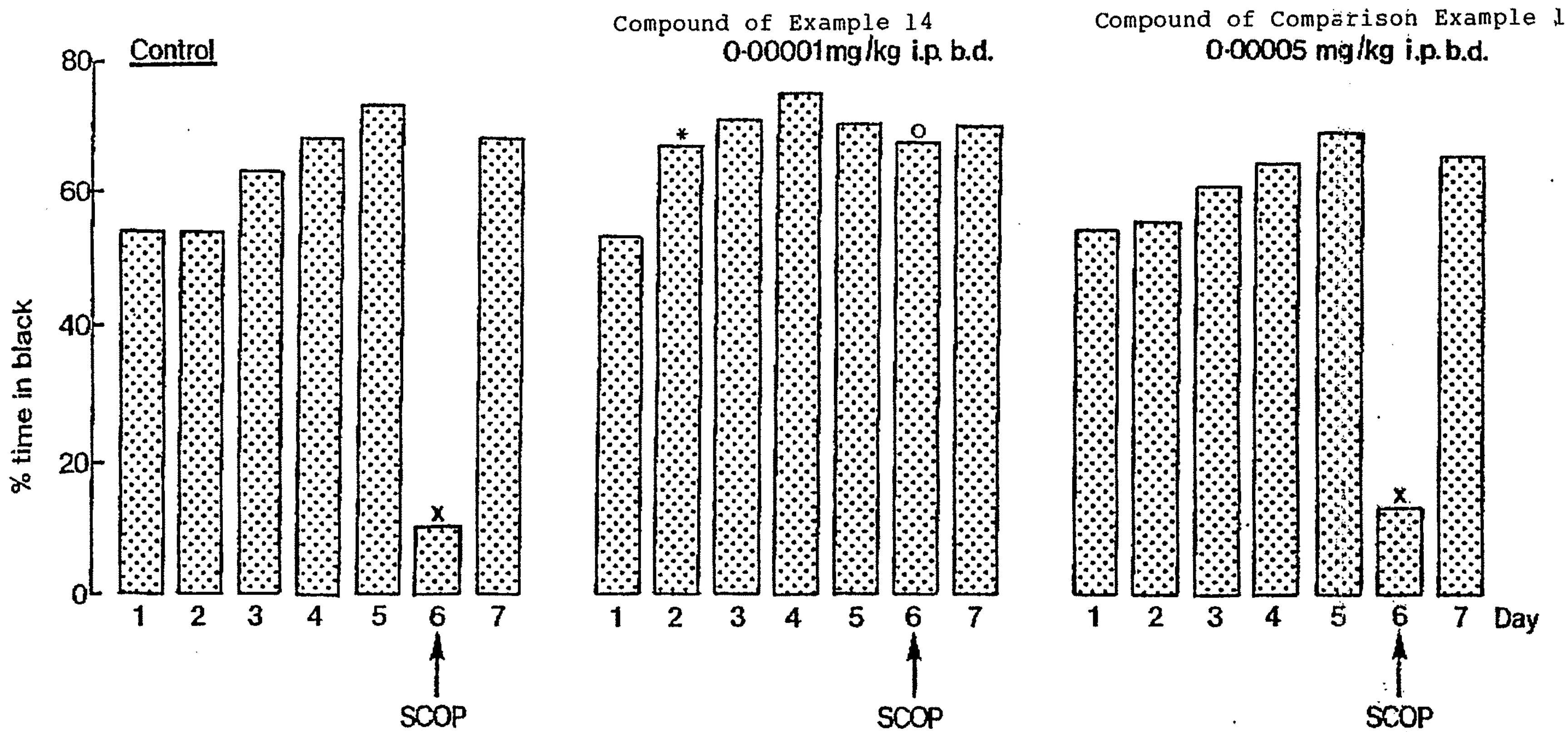

Control
Compound of Example 14
0·00001mg/kg i.p. b.d.
Compound of Comparison Example 1
0·00005 mg/kg i.p. b.d.
% time in black
80
60
40
20
0
1 2 3 4 5 6 7
Day
x
*
o
SCOP

FIGURE 2

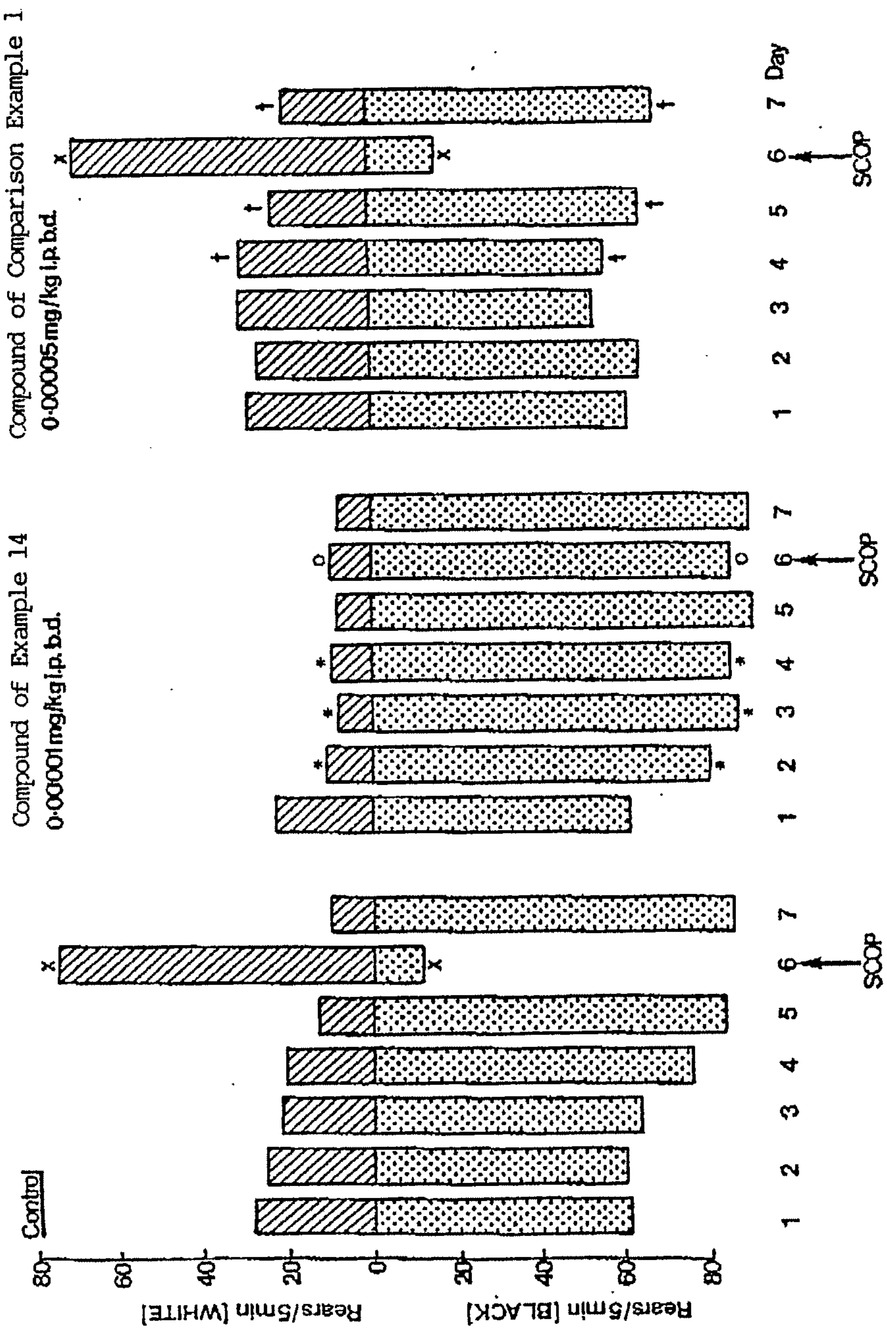

Control
Compound of Example 14
0·00001 mg/kg i.p. b.d.
Compound of Comparison Example 1
0·00005 mg/kg i.p. b.d.
Rears/5min [WHITE]
Rears/5min [BLACK]
80
60
40
20
0
20
40
60
80
1 2 3 4 5 6 7 Day
SCOP

FIGURE 3

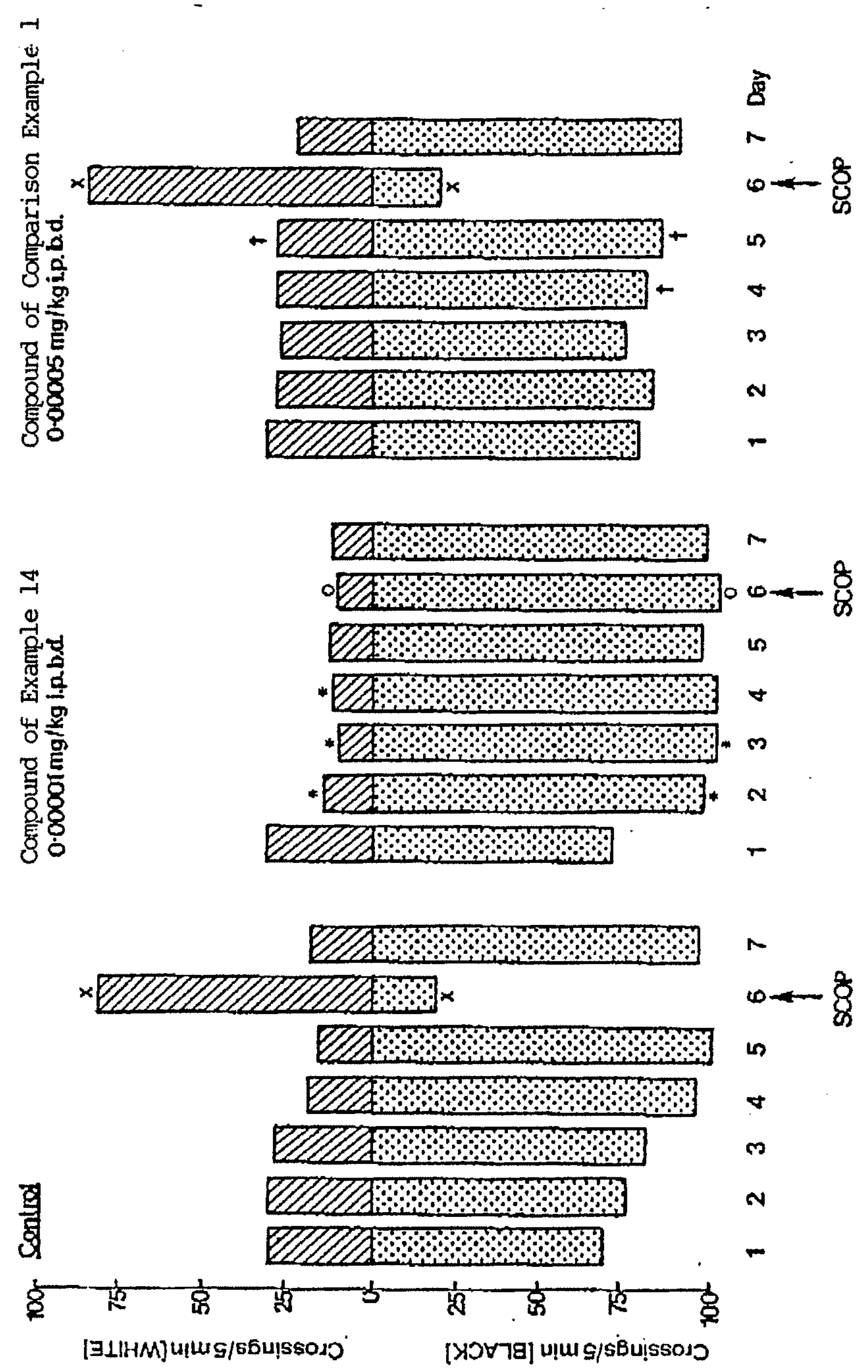

Control
Compound of Example 14
0·00001 mg/kg i.p.b.d
Compound of Comparison Example 1
0·00005 mg/kg i.p.b.d.
Crossings/5 min (WHITE)
Crossings/5 min [BLACK]
100
75
50
25
0
25
50
75
100
1
2
3
4
5
6
7
Day
SCOP

FIGURE 4

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 88 40 2041

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
D,X Y	EP-A-0 190 920 (ROBINS CO.) * Claims; page 3, lines 40-41; page 8, lines 21-30 * ---	1-4	A 61 K 31/435 A 61 K 31/505
Y	J. PHARM. PHARMACOL., vol. 40, April 1988, pages 301-302; W.W. SMITH et al.: "Zacopride, a potent 5-HT3 antagonist" * Whole article * ---	1-4	
Y	E. JUCKER: "Progress in Drug Research", vol. 30, 1986, pages 365-473, Birkhäuser Verlag * Pages 375-376, chapter 2.3: "Conformational analysis of 5-HT" * ---	1-4	
A	J. PHARM. PHARMACOL., vol. 40, April 1988, pages 302-305; M. COSTALL et al.: "Zacopride: anxiolytic profile in rodent and primate models of anxiety" * Abstract; page 303, figure 1 * -----	1-4	TECHNICAL FIELDS SEARCHED (Int. Cl.4) A 61 K 31/00

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	20-03-1989	ISERT B.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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